REMARKS

I. Introduction

In response to the Office Action dated September 16, 2002, claims 28 and 48 have been amended and claim 51 has been added. The amendments to claims 28 and 48 were made solely for the purpose of clarifying the language of the claims, and were not required for patentability or to distinguish the claims over the prior art. The amendments to claims 28 and 48 are fully supported by the specification and introduce no new matter. Amended claim 28 recites antibodies directed to a full length native sequence PRO285 polypeptide (comprising amino acids 1 to 1049) as disclosed for example at page 8, lines 15-28. Amended claim 48 recites antibodies directed to a native sequence PRO285 polypeptide lacking the putative 19 amino acid N-terminal signal peptide (see, e.g. page 18, line 10) and the transmembrane and intracellular domains as disclosed for example at page 8, lines 15-28.

Claims 28-30 and 48-51 remain in the application. Re-examination and re-consideration of the application, as amended, is requested.

II. Formal Matters

In response to the Examiner's comments at page 2 of the outstanding Office Action, Applicants have amended the title hereinabove.

In response to the comments regarding references 10-12 in the IDS filed 9/15/00 and references 4-9 of paper #13, Applicants respectfully note that to the extent that there is a duty to disclose the existence of such information, Applicants have met this duty by disclosing the sequences in the Information Disclosure Statements filed 9/15/00 and 6/27/01 (paper #13) and identifying them in the respective 1449 forms. The submission of these sequences meets the requirements for the submission of information set forth in 37 CFR 1.97 and 37 CFR 1.98.

III. Objections and Rejections Under 35 U.S.C. §101 and 35 U.S.C. §112, First Paragraph

On pages (4)-(5) of the Office Action, claims 28-30 and 48-50 were rejected under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph.

A. Claims Rejected Under 35 U.S.C. §101.

In the Office Action, the Examiner rejects the pending claims and states that while the asserted utilities with respect to preventing microbial binding are specific and substantial, they would not be considered credible by the skilled artisan. The Examiner challenges the credibility of Applicants' disclosure that PRO285 polypeptides are pathogen pattern recognition receptors that can sense the presence of conserved molecular structures present on microbes. In this utility rejection, the Examiner further notes that there is no disclosure of any ligand (e.g. bacteria) to which PRO285 binds.

Applicants respectfully traverse this rejection. Applicants respectfully submit that in view of the Patent Office guidelines promulgated to facilitate determinations of utility and a number of scientific articles concerning the state of the art relating to Toll homologues, the instant rejection should be withdrawn. Copies of the references that Applicants refer to below are provided herewith in Exhibit A or are provided in the accompanying Supplemental Information Disclosure Statement and Form 1449.

The standard for assessing credibility of an asserted utility is articulated in the guidelines promulgated by the Patent Office for the examination of applications for compliance with the utility requirement of 35 USC 101 and 35 USC 112, first paragraph (see, e.g. 60 Fed. Reg. 36263-02). In particular, Applicants direct the Examiner's attention to the portion of section 2(a) of these guidelines which is reproduced below:

> If the applicant has asserted that the claimed invention is useful for any particular purpose (i.e. a 'specific utility') and that assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility. Credibility is to be assessed from the perspective of one of ordinary skill in the art in view of any evidence of record (e.g. data, statements, opinions, references etc.) that is relevant to the applicant's assertions.

The guidelines dictate that the appropriate standard of review involves a determination of whether the asserted utility would be considered credible by a person of ordinary skill in the art. The guidelines further state that if the assertion would be considered credible by a person of ordinary skill in the art, the Patent Office must not impose a rejection based on lack of utility. Moreover, only after the examiner has provided evidence showing that one of ordinary skill in the art would

reasonably doubt the asserted utility does the burden shift to the Applicants (see, e.g. M.P.E.P. 2164.07).

Applicants first wish to briefly address the Examiner's comments at page 3 of the Office Action that there is no disclosure of any ligand (e.g. bacteria) to which PRO285 binds. Identification of a specific ligand is not an absolute requirement for finding utility of a newly identified receptor, such as disclosed in the present application. The ability to understand an activity or function of such a receptor can be understood in a variety of ways, absent the identification of a specific ligand binding partner. Those persons skilled in the art readily appreciate and understand that molecules that bind receptors can be used modulate ligand mediated signalling and that such molecules do not fail to be useful before that ligand is identified. For this reason, antibodies that modulate the binding interaction between pathogen pattern receptors (e.g. PRO285) and conserved molecular structures present on microbes are useful even before the specific molecular structure on the microbe is identified.

The utility (including the credibility of such utility) of the PRO258 molecules, and antibodies which bind to such PRO258 molecules that is provided in Applicants' application is further demonstrated by a number of scientific articles pertaining to the Toll polypeptide family.[1] In particular, the role that the Toll family of polypeptides play in sensing microbial pathogens was understood in the art, and this is shown by a review of Medzhitov et al., Nature 388, 394-397 (1997), Rock *et al.,* Proc. Natl. Acad. Sci. USA 95, 588-593 (1998) and Belvin and Anderson, Ann. Rev. Cell. Biol. 12, 393-416 (1996), all of which are cited in Applicants' specification and incorporated by reference therein. For example, Medzhitov et al.[2] teach that it is believed that the unique homology exhibited by the Toll polypeptide family results from their functional role in mediating ancient defense mechanisms that have been evolutionarily conserved in plants, insects and mammals (see, e.g. figure 1, page 394). Medzhitov et al. further teach that it is believed that this immune response has been preserved in vertebrates to induce signals that inform the adaptive system of the presence

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[1] It is proper to consider materials published after a critical filing date, for example when it is cited for the purpose of showing a fact under the principles of *In re Wilson*, 135 USPQ 442 (1962) (see, e.g. M.P.E.P. 2124).

[2] Medzhitov et al., is cited in Applicants specification for example at page 2, line 4.

of pathogens (see, e.g. page 396). Rock et al.[3] teach that Toll homologues are involved in innate immunity and that homology analyses of the human Toll gene family members TLR1, TLR2, TLR3, TLR4 and TLR5 as well as their biological association with the IL-1R-NF-κB pathway demonstrates that these Toll homologues are direct evolutionary counterparts of the Drosophila Toll genes. Rock et al. further teach that their homology and IL-1R-NF-κB pathway association provides evidence that the biological processes associated with Toll-Dorsal/IL-1R-NF-κB pathway are shared by both Drosophila and mammals. In this context, Bevlin et al.[4] teach that "[t]hus far the only biological process common to Drosophila and mammals that uses the Toll-Dorsal/IL-1R-NF-κB pathway is innate immunity—the rapid and nonspecific response to pathogens that leads to the production of antimicrobial peptides and cytokines". Accordingly, such teachings, e.g., (1) the unique homology between Drosophila and mammal Toll polypeptides; (2) the association between these molecules and the IL-1R-NF-κB pathway; and (3) the fact that the only biological process common to Drosophila and mammals that uses the Toll-Dorsal/IL-1R-NF-κB pathway is the innate response to microbial pathogens, further support the teaching in the present application that PRO285 molecules are involved in the response to microbial pathogens.

The Examiner specifically states that skilled artisans would not believe that Applicants' data regarding TLR2 is predictive for homologous proteins such as PRO285 (e.g. the data presented in Example 11 which implicates TLR2 in the transduction of signals evoked by Gram-positive bacteria). Applicants respectfully disagree and direct the Examiner's attention to Du et al., Eur. Cytokine Netw. 11(3), 362-371 (2000), which describes the isolation of three mammalian toll-like receptors.[5] According to Du et al., functional data relating to one Toll family member such as TLR2 can reasonably suggest functions of other Toll homologues. In discussing the rationale for identifying novel toll-like receptors, at page 363, Du et al., explicitly teach:

> The Tlr2 gene product was subsequently implicated in the transduction of signals evoked by Gram-positive bacteria [19],

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[3] Rock et al., is cited in Applicants specification for example at page 2, line 25.

[4] Belvin et al., is cited in Applicants specification for example at page 50, line 11.

[5] Applicants note that this reference was published after Applicants' filing date, and that it is cited for the purpose of showing a fact (e.g. demonstrating what skilled artisans believe to be credible in view of certain types of data) under the principles of *In re Wilson*, 135 USPQ 442 (1962).

> and knockout work has provided evidence that signaling initiated by peptidoglycan (muramyldipeptide) and at least some lipopeptides are both dependent upon this receptor [18,20]. Hence, Tlr2, like Tlr4, may be oligospecific rather than monospecific. **It is plausible to think that other bacterial products signal via other Tlrs, and that in this manner, the Tlrs may collectively be responsible for the sensing of virtually all microbial pathogens.**
> For this reason, there has been a compelling motive for identifying novel Tlrs (emphasis added).

For at least the reasons above, the Examiner's position that Applicants' asserted utility lacks credibility is in direct conflict with the evidence concerning the state of the art - i.e., that bacterial products can signal via Toll family homologues (e.g. PRO285) and that members of this family of proteins may collectively be responsible for the sensing of virtually all microbial pathogens. Applicants respectfully request the withdrawal of the rejection under 35 U.S.C. §101.

B. Rejection under 35 U.S.C. §112, First Paragraph.

In rejecting the claims under 35 U.S.C. §112 at page 4 of the outstanding office action the Examiner further asserts "since the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention."

As discussed above, the asserted utility is credible. Consequently, one skilled in the art clearly would in fact know how to use the claimed invention. For this reason, Applicants respectfully request the withdrawal of the rejection under 35 U.S.C. §112 first paragraph.

IV. Objections Under 35 U.S.C. §112, Second Paragraph

On page 5 of the Office Action, Claims 28-30 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Applicants have amended claim 28 in accordance with the Examiner's suggestion in order to overcome this rejection.

V. Rejection under 35 U.S.C. §102(b)

On page 5 of the Office Action, claims 28 and 48 were rejected under 35 U.S.C. §102(b) as being anticipated by Ruggeri et al., WO 91/09614 (Ruggeri). In pages (5)-(6) of the Office Action, claim 50 was rejected under 35 U.S.C. §103(a) as being unpatentable over Ruggeri in view of Coughlin, U.S. Patent No. 5,256,766 (Coughlin), and further in view of Ladner et al., U.S. Patent No. 4,946,778 (Ladner).

The Ruggeri reference discloses peptides and other polymers which inhibit the binding of von Willebrand factor to platelet membrane glycoprotein Ib and/or glycoprotein Ib expressed on the surface of any cell of megakaryocyte lineage and methods of inhibiting platelet activation, adhesion of platelets to surfaces, platelet aggregation, or thrombosis. A 9 amino acid segment of the 45 kDa amino terminal region of platelet membrane glycoprotein Ib that is shown in figure 1 of the Ruggeri reference is identical to a 9 amino segment present in the PRO285 polypeptide that is disclosed in the instant application.

The Examiner asserts that Ruggeri et al. disclose a 19 residue peptide that matches SEQ ID NO: 2 at positions 704-712, a 9/15 match and that at page 19 and in claim 65, antibodies to such peptides are disclosed and claimed.

As this is a rejection under 35 U.S.C. §102(b), the Examiner is asserting that the antibodies of the Ruggeri disclosure anticipate the antibodies recited in claims 28 and 48.

Applicants respectfully traverse the rejection because the Ruggeri disclosure does not teach or enable the subject matter recited in the instant claims. First, as the Ruggeri reference fails to disclose PRO285 polypeptides, much less antibodies thereto, this reference cannot explicitly teach antibodies that bind to a PRO285 polypeptide. In addition, the Ruggeri disclosure cannot anticipate the claimed invention via inherency because there is no suggestion by Ruggeri that an antibody that binds to a PRO285 polypeptide can be generated using the 19 residue GPIbα peptide as an immunogen.

When articulating the legal requirements for a finding of anticipation via inherency in contexts such as those involving unpredictable biological processes, courts state that inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991). Instead, to establish inherency, the extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co.*, 948 F.2d at 1268.

As noted above, an antibody which binds a PRO285 polypeptide is not necessarily disclosed in the Ruggeri disclosure, and thus this reference fails to meet the legal requirements for anticipation via inherency. For these reasons, Applicants respectfully request the withdrawal of the rejection under 35 U.S.C. §102(b).

VI. Conclusion

In view of the above, it is submitted that this application is now in good order for allowance and such allowance is respectfully solicited. Should the Examiner believe minor matters still remain that can be resolved in a telephone interview, the Examiner is urged to call Applicants' undersigned attorney.

Respectfully submitted,

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APPENDIX: CLAIMS IN MARKED-UP FORM

28. (THREE TIMES AMENDED) An isolated antibody which [specifically] binds to a PRO285 polypeptide comprising amino acids 1 to 1049 encoded by [DNA 40021 (]SEQ ID NO:2[)].

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30. (TWICE AMENDED) The antibody of claim 29 which blocks [the recognition of] binding of said polypeptide to a Gram-negative or Gram-positive organism [by said polypeptide].

48. (AMENDED) An isolated antibody which [specifically] binds to a PRO285 polypeptide consisting of amino acid residues [30] 20 to 836 of Fig. 1 (SEQ ID NO:1).